Global Regulatory Policy

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Division of Drug Information (HFA-240)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: Docket No. 2003D-0497 - Draft Guidance for Industry: Pharmacogenomic Data Submissions

Merck & Co., Inc is a leading worldwide, human health products company. Through a combination of the best science and state-of-the-art medicine, Merck's Research and Development (R&D) pipeline has produced many important pharmaceutical products available today. These products have saved the lives of or improved the quality of life for millions of people globally.

We have established a focus on drug development that leverages knowledge derived from the human genome and cutting-edge genomics technologies to produce the next generation of therapeutics. The regulation of these genomics-based products currently in development at Merck & Co., Inc. will benefit from the approaches outlined in this draft guidance. As such, we welcome the opportunity to provide our comments to this important draft document. This guidance will provide the framework to help the innovator determine the best approaches to reporting genomic data to the Agency.

We appreciate the continued focus of the Agency on innovative approaches to the regulation of biologics and drugs from early development to post-approval changes. We fully support development of this guidance document. The comments that we are providing are intended to enhance the information found in the draft document and expand its usefulness. Our comments are divided into General Comments and Regulatory Comments and incorporate a dual focus: preclinical and clinical.

General Comments

Need for International Harmonization: As a global pharmaceutical company, Merck supports harmonization of regulatory approaches whenever possible. The concept of establishing a worldwide regulatory pathway for voluntary submission of exploratory pharmacogenomics data would facilitate the overall acceptance of the concept in the US. The same reasons for a sponsor to submit voluntarily preliminary, unconfirmed data to the FDA also apply internationally: as an educational tool to support regulator's experience in handling genomic data and to provide clarity in the approach the sponsors

should take in deciding to submit these data. Establishing a worldwide harmonized approach to pharmacogenomics data submission may be facilitated by the newness of the science as established pathways are nonexistent. We support FDA's efforts in moving toward a harmonized approach to genomics regulation.

Format of the Draft Guidance: We recommend that the guidance document be separated into two distinct sections encompassing Preclinical and Clinical Genomic Data. Greater clarity in the guidance document would be achieved if clinical applications of pharmacogenomics data were segregated completely in a revised guidance document from animal based applications involving pharmacogenomics data generation.

Definition of Pharmacogenomics: In the explanation of the statement of purpose, the term *pharmacogenomics* is defined as "the use of a pharmacogenomics or pharmacogenetic test in conjunction with drug therapy". The definition emphasizes the use of pharmacogenomics for patient treatment and therefore appears to include only human clinical aspects of genomics. We suggest modifying the definition to include the use of pharmacogenomics in preclinical drug development. The definition may be expanded by the following addition to the text: "the use of a pharmacogenomics or pharmacogenetic test in conjunction with drug **development** and therapy". A working definition of the term pharmacogenomics achieved broad consensus in the first FDA/industry genomics workshop (May 2002) and we propose consideration of that definition in this draft guidance.

Definition of Clinical Biomarkers: We recognize that the use of biomarkers is not specific to drug development guided by the use of genomics and we agree with the need to define it to encompass the broad meaning of the term. The clear definition of these biomarkers is imperative since they are at the center of key decision points for sponsors in the decision trees described in the text and in Appendices A, B, and C. To improve the clarity of the draft document, we suggest a binary system of nomenclature that is consistent with the spirit of the guidance, specifically a categorization of biomarkers as **"valid biomarkers"** and **"exploratory biomarkers"** (or "candidate biomarkers", "research biomarkers" etc.). Eliminating the category of "probable valid biomarker" would lead to simplification of the decision-making process. For example, it would eliminate decision point 5 in Appendix A since it would be implied by decision point 4 (Lines 661 and following), and would eliminate decision point 3 in Appendix B and be covered by the language in decision point 4 (Lines 712 and following). All studies using the category of probable valid biomarker would be considered "exploratory biomarkers' in our scheme and constitute "general exploratory or research information" (Line 715). This would imply that it would be up to product sponsors to decide whether to submit exploratory studies not used in decision making to the Agency using the voluntary genomic data submission (VGDS) approach. This model would be compatible with eventual elevation of exploratory biomarkers to valid biomarkers. For example, as VGDS data accumulated regarding a biomarker and analytical test system, the data might be

referred to the proposed biomarker Advisory Panel (see below) for approval as a valid biomarker or back to the scientific community for additional data.

We agree that concurrence on valid biomarkers is not without difficulty, but we propose that the Agency consider establishing a formal way of evaluating these biomarkers as well as communicating a list of valid biomarkers and their associated analytical tests. This list could be agreed to by a Genomics Advisory Panel with experts selected by the Agency and including appropriate industry representation. The panel agreeing to the status of a biomarker as "valid" will need to have expertise in the area of analytical development (to assess that the analytical test system has "well-established performance characteristics") and have the necessary medical expertise to validate the clinical significance of the biomarker. Clearly a transparent process, including a request for public comment on the proposed elevation of a biomarker to valid status, would need to be established.

Biomarkers in Preclinical Development: At present, there is the widespread notion that all gene expression changes from animal studies are exploratory and hypothesis generating measurements that may be used to define followup investigative studies. Only after efforts are made in followup studies can the value of the initial exploratory studies be confirmed. If no pharmacogenomics biomarkers from animal studies can be defined as "valid", then the point of establishing any difference between valid and exploratory is moot. However, if the Agency envisions that biomarkers from gene expression studies in animals eventually will become sufficiently well established to support a significant association to a safety outcome, a means of communicating these valid preclinical biomarkers is needed. We propose that a similar Advisory Panel as described in our comments above be assembled to evaluate biomarkers in preclinical development employing a transparent process and active communication to the pharmaceutical industry.

We suggest that line 262 requires further clarification – pharmacogenomic data from animal studies ordinarily should be submitted under 312.23(a)(8) when ...the test is well established as a predictive biomarker. The CFR reference specifies that a full report must be submitted to the IND only if the data are used to support the safety of the proposed clinical investigation. The use of the word "or" in line 262 of the draft guidance suggests that an abbreviated report should also be submitted when the test is well established as a predictive biomarker even if the sponsor is not using these data to make a scientific case. For animal studies, there needs to be more clarity as to what constitutes a "test" or "predictive biomarker". Preclinical pharmacogenomic testing could include single transcript changes of a defined magnitude, changes in groups of small numbers of transcripts in a complex dynamic manner, or changes in patterns of large sets of transcripts identified by a complex mathematical algorithm.

Preclinical Data Requirements: We believe there is a need to resolve an apparent conflict between the requirements to generate data from non-clinical studies under GLP's

to support safety findings, as described in 21 CFR Part 58, and the concept that only some of the data generated, using a broad pharmacogenomic test system such as a microarray, could be defined as valid biomarkers. We recommend that only where data will be used to replace current standard safety testing paradigms or where prospective measurement of the valid biomarkers has become an established regulatory requirement should GLP compliance be required.

It is reasonable to expect, however, that core sets of transcripts that a sponsor has discovered from followups to initial exploratory studies may be considered exploratory biomarkers. These could support a scientific argument pertaining to improved understanding of the safety of the drug, and could require independent confirmation using an analytical method that is 21 CFR Part 58 compliant.

We propose that, at present, all broad genome scale measures of gene expression changes using array platforms be considered exploratory. Submission of such broad data sets should remain voluntary. Should sponsors choose to base a safety decision on changes in key sets of the thousands of transcripts from microarray experiments from animal studies, these measurements should be independently analytically validated. This select and understood data subset should be submitted. The Agency will learn together with sponsors from these highly reliable data sets. As the Agency learns of core sets of transcripts that reliably convey a convincing safety concern, these transcripts will evolve to the status of known valid biomarkers. Over time the set of known valid transcript biomarkers will grow.

We agree with the Agency that there are two fundamental determinants to guide genomic data submission: – (1) the purpose of the study and of the test within the study, and (2) the validated stature of the measurement. For exploratory research or a compound screening study, we agree that submission of data be voluntary. When the animal study is performed for the purpose of generating data that will inform the safe conduct of a clinical trial, but the data from the measurements are exploratory and not sufficiently validated to be relied upon, then data submission should also be voluntary. When the animal study is performed for the purpose of generating data that will inform the safe conduct of a clinical trial, and the data from the measurements taken are sufficiently validated to be relied upon by the sponsor, then those validated data subsets should be submitted. Such a strategy would facilitate progress in the field of animal based applications of pharmacogenomics.

Regulatory

Document Submission: In the instance when a sponsor has an active IND and a market application (approved or pending), it is unclear to which file the Agency prefers VDGS to be submitted.

Pre-submission Meeting and Timing: We suggest that the Agency describe an optional mechanism for communication with sponsors prior to voluntary genomic data submission. It will be important for the Agency to be fully briefed prior to receipt of the data package. This information exchange between the sponsor and the Agency will be especially critical when the data are generated in preclinical models prior to the establishment of an IND. In the situation where an IND is not yet opened, we have concerns about the intellectual property protection afforded to data submitted to the Agency. We recommend that the Agency clearly address this issue in the guidance. In the spirit of advancing the science of pharmacogenomics, we recommend that the Agency act favorably on requests for such meetings and not necessarily subject them to PDUFA-goals.

Interdisciplinary Pharmacogenomic Review Group: Merck strongly supports the concept of an Interdisciplinary Pharmacogenomic Review Group (IPRG) to review VGDS submissions. We believe this will strengthen and facilitate the review of applications (by the formal review divisions) containing required pharmacogenomic data. The cadre of experts forming the IPRG should be comprised of representatives from all Centers: CBER, CDER and CDRH. We recommend the Agency provide additional guidance on the membership and role of the IPRG including how the IPRG will review submissions, and how working conclusions drawn from such reviews are communicated back to product sponsors and the review divisions. We suggest that the communication flow between the IPRG and the review divisions (Project managers) be clearly defined. For the interaction between sponsors and the IPRG, we propose a delineated, and perhaps optional, process be described for sponsors to interact with the IPRG and the Review Division on pharmacogenomics issues. Such a process would utilize the IPRG appropriately in the way the Agency intended, to advance the understanding of pharmacogenomic data by sponsors and the Agency.

We think the Guidance is clear that if a body of evidence accumulated within the IPRG regarding pharmacogenomic data raised concerns about the safety or efficacy of a therapeutic class, then the Agency will "notify sponsors about this determination" (Line 506). We agree with this approach and appreciate that this is not different than the current approach to new safety or efficacy concerns that are discovered in investigational products. We believe that these concerns should be transmitted promptly to sponsors. However, we would highlight the fact that the validity and the quality of the analytical test systems to measure exploratory biomarkers will be less than that of traditional biomarkers. Thus, we would urge significant caution before conclusions are drawn by the IPRG that would lead to regulatory action against the sponsor or other sponsors with developmental compounds in the same therapeutic class. We recommend that the Agency confer with the sponsor if there were uncertainty regarding data quality, results, or conclusions regarding the VGDS submission, especially as these impact the IPRG's conclusions about whether a safety issue is present.

Data Quality and Format: The Guidance should clarify that the collection of clinical supportive data from pharmacogenomic biomarkers, even if used in a full data submission or abbreviated report, should be collected under conditions according to FDA standards for clinical trial data. Other standards such as GLP or conditions that might be used for an IVD-supportive trial should not be applied automatically, unless appropriate, for example, if the sponsor were intending to submit data to the CDRH or joint committee supporting utilizing pharmacogenomic test as a pre-prescription label requirement.

With regard to VGDS submissions format, we appreciate the template provided by the Guidance starting on Line 441 and believe it contains many useful elements. We recommend that the Agency seek external input for future pharmacogenomic templates, for example, for pharmacogenomic reports using DNA-based polymorphisms. These inputs could be solicited from sponsors or other external entities with expertise in the field. As the IPRG identifies data elements and formats that it finds useful, we recommend that these are communicated in a public forum.

As additional principles for acquisition of pharmacogenomic data, validation of pharmacogenomic data/ biomarkers, submission of data, statistical analysis of pharmacogenomic data and uses of pharmacogenomic data in product development become "state of the art" within the Agency, we propose that these be transparently communicated in future guidance documents.

Editorial Comments

(Line 299) We suggest changing "single-nucleotide polymorphism (SNP)" to "**DNA polymorphism**" or some other term, to allow for non-SNP polymorphisms such as insertion/deletions, tandem repeats, etc.

Throughout the guidance, the Agency should consider replacing the term "unapproved" NDA/BLA with "**pending**" NDA/BLA.

We appreciate the opportunity to share our comments with respect to FDA's Draft Guidance for Industry: Pharmacogenomic Data Submissions. Please do not hesitate to contact me, should you have any questions.

Sincerely,

for Donald M. Black, MD, MBA
Vice President
Global Strategic Regulatory Development